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VARICELLA-ZOSTER VIRUS DISEASE AND EPIDEMIOLOGY: SEEKING BETTER CONTROL STRATEGIES – PART 1*

Introduction

The purpose of this two-part series is to review strategies for the control of varicella-zoster virus (VZV) infection and ongoing related public-health discussions in Canada. This part focuses on the clinical and epidemiologic description of varicella-zoster virus disease and summarizes the epidemiologic data available through routine national surveillance in Canada. Part 2, to be published in an upcoming issue, will review strategies for control of VZV infection, including those used in countries where a licensed vaccine is available, as well as highlight developments in Canada for introducing a control strategy.

Historical perspective and clinical features

It is now well recognized that VZV causes two clinical diseases: varicella (chickenpox) and zoster (shingles). In early medical literature, zoster was described as an independent of varicella while the latter was often confused with smallpox until the 1760s when the clinical differentiation between smallpox and chickenpox was made[1]. As recently as 1940, it was taught at Harvard University that zoster and chickenpox were distinct and unrelated[2]. Following its concurrent isolation from patients with varicella and zoster, by Thomas Weller and his colleagues, VZV was definitively described in 1958 as the etiological agent for the two clinical entities[1,2].

Varicella is a highly contagious disease caused by primary VZV infection and characterized by a short or absent prodromal phase, followed by fever and a characteristic pruritic rash. Figure 1 illustrates the typical clinical course of varicella. The rash appears in crops, progressing rapidly from macules to papules, vesicles, pustules, and eventually to crusted lesions. Typically, three successive crops of lesions, ranging between 250 and 500 lesions in total, appear over a 3-day period. Therefore, a combination of all five types of lesions may present during the peak of the clinical phase[1,3]. The rash is centrally distributed with lesions concentrated on the trunk, scalp, and face. Diagnosis of varicella can be made clinically by the characteristic rash and epidemiologic factors, such as a history of susceptibility and known exposure to a person with varicella or zoster. Second attacks may occur but are unusual and mostly mild[3].

The virus is spread by airborne droplets and by direct contact with respiratory secretions or vesicular fluid, with an incubation period averaging 14 to 16 days (outside limits of 10 to 21 days)[3]. The infection is highly contagious, with infectivity highest 1 to 2 days before the onset of the rash and up to 5 days after the first crop of lesions appear or when all lesions are crusted. It is estimated that in most temperate countries, > 90% of individuals are infected by 14 years of age[4]. Secondary attack rates are estimated at 90% and 96% for susceptible household contacts[1,5,6].

Complications of chickenpox are rare in immunocompetent children, with < 2 deaths per 100,000 cases in children 1 and 14 years of age reported[1,4], while chickenpox-associated complications and deaths (up to 25 per 10,000 cases[6]) are more

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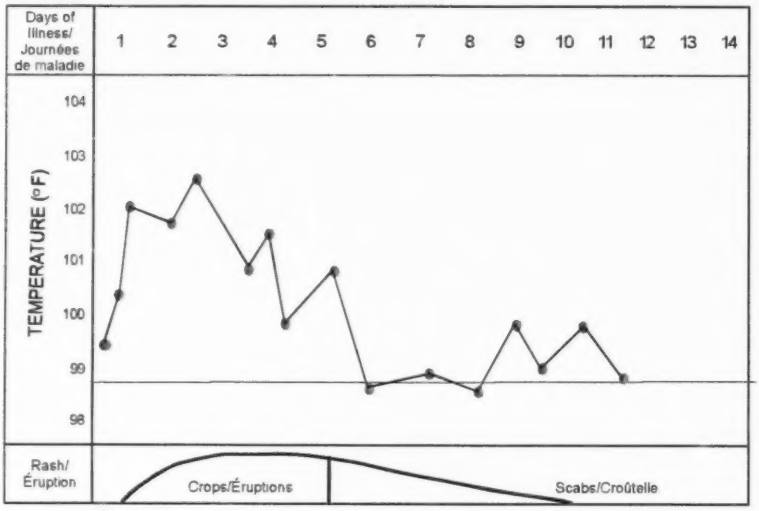
Figure 1
Schematic diagram illustrating the typical clinical course of chickenpox*



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frequent in adults. In population-based studies in the United States, the most common complications in hospitalized persons were secondary bacterial infections, Reye's syndrome, pneumonia, and encephalitis in persons < 15 years old, and pneumonia and encephalitis in those ≥ 15 years old[7,8]. Age-specific data for the United States, from 1972 to 1978, show that persons aged ≥ 20 years old comprised < 2% of cases but accounted for 11.6% of varicella encephalitis and 27.6% of varicella-related deaths[9]. Similar data for 1990 to 1994 reported < 5% of varicella cases but 55% of varicella-related deaths in persons > 20 years of age[10]. Varicella encephalitis is associated with mortality of about 10% and up to 15% sequelae in survivors[4]. Recent reports of concurrent infection with varicella and invasive Group A *Streptococcus* provide further evidence that the risk of invasive Group A streptococcal disease increases after chickenpox[11,12]. VZV infection in immunodeficient individuals, particularly those with severe impairment of cell-mediated immunity, is often serious and potentially fatal, contrasting with the relatively benign and self-limited illness (lasting 4 to 5 days) in immunocompetent persons in younger age groups.

Zoster results from reactivation of latent VZV acquired during chickenpox. Zoster is characterized clinically by a painful, unilateral, vesicular rash in a dermatomal distribution, lasting a few days to several weeks; occasionally patients with zoster will not have a rash. Although the rash typically remains localized to one to three dermatomes, in a minority of patients it disseminates outside the dermatomal area and causes widespread lesions that resemble varicella. The factors that control whether the virus remains latent are not well understood; however, a low cell-mediated immunity to VZV in the presence of normal humoral immunity appears to be a necessary but insufficient setting for the development of zoster[1]. Zoster occurs more frequently in the elderly than the young, with a sharp increase in incidence at about 50 years of age, and is also more common in immunocompromised than immunocompetent persons[1]. Postherpetic neuralgia, developing at least 1 month after the onset of the zoster rash and lasting up to 1 year, is described as a dreaded complication of zoster, with severe, lancinating, or boring pain. It is believed to be due, at least in part, to scarring of virus-injured nerves undergoing regeneration[1]. There is a strong correlation between postherpetic neuralgia and increasing age of zoster patients. Patients with zoster remain infectious to persons who have not had chickenpox as long as new lesions remain moist; the virus is present in skin lesions but does not appear to be carried to the respiratory tract therefore transmission is by direct contact.

Congenital varicella syndrome occurs uncommonly following maternal infection with VZV during pregnancy; it is estimated to occur in 2% of maternal varicella cases and even more rarely after maternal zoster. The clinical manifestations of congenital varicella syndrome are well documented, consisting typically of dermatomal skin scarring overlying a hypoplastic limb and a variety of neurological defects[1,3]. Infants with the syndrome may develop recurrent vesicular zoster-like skin lesions which may be the only evidence of congenital infection when maternal infection occurs late in pregnancy. Maternal varicella infection within 5 days before or 2 days after delivery greatly increases the risk of severe or fatal infection in the newborn. This is attributed to insufficient protective maternal antibodies and presumably the immaturity of

cell-mediated immunity in the newborn[1,3]. The potentially fatal illness in the newborn can be avoided or mitigated by prompt passive immunization with varicella-zoster immune globulin.

Epidemiology of chickenpox in Canada

Chickenpox was a nationally notifiable disease between 1924 and 1958, and was reintroduced on the list of notifiable diseases in 1986[13]. Since 1986 however, reporting of chickenpox to the Laboratory Centre for Disease Control (LCDC) from the 12 provinces and territories has never been universal; the number of jurisdictions reporting cases between 1986 and 1998 has ranged between eight and 10. Currently, incidence data are only available for Newfoundland, Nova Scotia, New Brunswick, Prince Edward Island, Ontario, Alberta, Yukon, and the Northwest Territories, comprising 55% of the Canadian population. The mean crude annual incidence rate of varicella from 1992 to 1996 (based on reporting jurisdictions) is 240 cases per 100,000 population, ranging between 126 and 301 cases per 100,000 population (LCDC: unpublished data). The actual number of cases reported annually for 1992 to 1996 ranged between 17,788 and 50,836; projected to the overall Canadian population, the estimated mean annual incidence would be 69,200 cases. Because of the high level of contagiousness, estimates of annual varicella incidence are inferred to approximate the annual birth cohort[1]. Thus, approximately 380,000 varicella cases can be projected in Canada annually, meaning that the current level of reporting in reporting jurisdictions is < 20% of the expected number of cases.

Approximately 34% of reported cases from 1992 to 1996 were < 5 years of age, 86% < 10 years of age, and 95% < 15 years of age. The mean annual age-specific incidence was highest in school-age children 5 to 9 years old (1,874 per 100,000 population) followed by children 1 to 4 years old (1,118 per 100,000 population), those 10 to 14 years old (384 per 100,000 population), and infants < 1 year old (367 per 100,000 population). The overall age distribution is similar to that reported in Canada in the mid-1980s[13] and in the United States for 1980 to 1990[6]. Physician compliance with reporting may be biased towards younger children, contributing to the higher incidence in younger age groups.

Prevention of varicella

In Canada, the post-exposure management of varicella continues to consist of the administration of varicella-zoster immune globulin to susceptible individuals whose risk of serious morbidity or mortality is substantially increased and the use of anti-viral therapies. A live attenuated Oka-strain varicella vaccine was first developed in 1974, and vaccines are licensed in Japan, Korea, several European countries, and the United States. The safety, immunogenicity, and efficacy of the vaccine have all been reported as favourable in both healthy and leukemic children[6,14,15]. The post-licensure effectiveness of the American-licensed varicella vaccine has been estimated as 86% against all forms of varicella and 100% against moderate-to-severe disease[15]. There is currently no licensed vaccine in Canada. LCDC plans to hold a consensus conference in collaboration with various public-health partners in early 1999 to discuss control strategies for varicella in Canada. It is also expected that the results of cost-benefit analyses of routine varicella vaccination in the Canadian health-care system will be available by early 1999.

Public-health significance

The burden associated with varicella and zoster in Canada have not been well documented in the published literature. Childhood chickenpox is often associated with school absence for the child as well as loss of work days (and lost productivity) for primary caregivers. One study in the United States reported lost work days for two-thirds of working mothers (average of 2.5 days) and one-third of working fathers (average of 0.8 day) during a 12-month period[16]. Lost work days are even more prolonged with adult chickenpox because of more severe illness and the likelihood of hospitalizations for complications. Uncomplicated cases of varicella or zoster can also lead to work loss for susceptible or infected health-care workers who present a danger to immunocompromised patients; furloughing of such employees can be a real strain on health care and hospital budgets. Additional health-care costs to individuals or society accrue from hospitalizations for complicated cases. Finally, cases of congenital varicella syndrome, while rare, can be associated with prohibitive lifetime costs. All of these factors add to the total burden of VZV which may be substantially reduced if disease incidence and morbidity can be reduced through vaccination.

In a historical and clinical review paper on varicella published in 1996, Thomas Weller, who with his colleagues first isolated VZV, noted[2], "VZV can no longer be classified as producing a benign disease. As we discuss indications and the need for varicella vaccine, the increasing importance of the illnesses produced by this reclusive virus per se constitute a persuasive argument for its use."

This observation may be particularly relevant to the Canadian public-health community as we debate the potential for introducing routine vaccination against varicella. Whether a routine vaccination program will be introduced and what the targeted population will be for a publicly funded program will be influenced not only by vaccine licensure but also by a number of the usual considerations for implementing public-health programs: desired program objectives, benefits and risks of the vaccination program, program costs in relation to benefits, and competing budgets for introducing or expanding other vaccination and public-health programs. The second article in this series will highlight some of the arguments for and against introducing routine varicella vaccination (including vaccine effectiveness, vaccine safety, and cost-benefit considerations) based on the experience of other countries.

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Source: *A Bentsi-Enchill, MB, ChB, MSc, Division of Immunization, Bureau of Infectious Diseases, LCDC, Ottawa, ON.*

Editorial Note

Additional epidemiologic data are available for cases hospitalized in 11 pediatric hospitals which comprise the IMPACT (Immunization Monitoring Program ACTive) surveillance system and are due to be published by the IMPACT investigators. As well, a number of studies on the epidemiology of VZV infections and their public-health impact in Canada are ongoing and will be a valuable source of further information.

International Notes

DISEASE SURVEILLANCE – WHO'S ROLE

Since 1992, alarm over emerging and re-emerging diseases has resulted in a number of national and international initiatives to restore and improve surveillance and control of communicable diseases. In 1995, the World Health Assembly urged all Member States to strengthen surveillance for infectious diseases in order to promptly detect re-emerging diseases and identify new infectious diseases, recognizing that success depended on the ability to obtain information on infectious diseases and the willingness to communicate this information nationally and internationally.

One of WHO's main means of creating a global surveillance system has been the development of a "network of networks" which links together existing local, regional, national, and international networks of laboratories and medical centres into a super surveillance network. This network is being constructed together with the 191 WHO Member States and other partners, including the European Union-United States Task Force on Emerging Communicable Diseases and the US-Japan Common Agenda; the network has also been cited as an area of collaboration by the G-7 and G-8 member countries at both the Lyon (1996) and the Denver (1997) Summit meetings.

A practical example: global influenza surveillance

Influenza surveillance is one of the most developed global surveillance and monitoring systems of WHO. It started in 1948 and has developed over the years into a highly successful global partnership. The network now involves 100 collaborating laboratories in 82 countries, constantly monitoring locally isolated influenza viruses and providing information on true emergence and spread of different strains. National case detection systems and laboratories have been strengthened by WHO and its partners using internationally accepted norms, and virus isolates from the national laboratories are analyzed in more detail in one of the four WHO collaborating centres for influenza. The data are then used by experts associated with the surveillance system to make recommendations on the three virus strains to be included in the next season's influenza vaccine. Thus, information generated from global surveillance results in an important and unified public-health response each year. The annual design of the vaccine also represents an outstandingly successful collaboration between the public and private sectors.

In parallel to the surveillance program, national and global pandemic plans are being developed to systematically address the next influenza pandemic. Both the surveillance system and the elements of the global pandemic plan were tested during the outbreak of the avian influenza A(H5N1) virus in human subjects in Hong Kong (Special Administrative Region of China) in late 1997. The rapid identification of the virus strain in one of the collaborating laboratories in the Netherlands, followed by the mobilization and coordination of an investigating team from WHO

collaborating centres in the United States, extensive epidemiologic and laboratory studies, the prompt dissemination of public information, the development of diagnostic test kits for international distribution, and the identification of a virus line suitable for vaccine development all contributed to a timely, ordered, and effective response to the outbreak.

WHO'S epidemic preparedness and response

Once a communicable disease outbreak has been confirmed, pertinent information is published in the *Weekly Epidemiological Record* and placed on the Web, where it can be accessed by the general public at <http://www.who.int/emc/>. At the same time, an international response, with the input of technical and humanitarian partners, is mounted if required. A WHO team arrives on site within 24 hours of outbreak confirmation to make an initial assessment, begin immediate control measures, and prepare the ground for the larger international response if needed. By linking the international response to systematic global surveillance, a worldwide network is available from which to solicit support, thus ensuring that no one country, or technical or humanitarian partner must bear the entire burden.

Source: *WHO Weekly Epidemiological Record, Vol 73, No 43, 1998.*

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